REMARKS

Claims 1-2 and 4-9, 12-18, 20-24, 27 and 31-37 are pending. Applicant has amended claim 37 to delete the term cytokine and replace it with "interleukin-2". Basis for this amendment can be found in the specification on page 5, line 26. Applicant submits no new matter is introduced by this amendment and that the claims 1, 2, 4-9, 12-24, 27 and 31-37 are in condition for allowance.

Non-statutory Double Patenting Rejection

Applicant acknowledges that the non-statutory double patenting rejection is held in abeyance in this application.

Rejection of Claims Under 35 U.S.C. §112(2)

The Examiner has rejected claim 37 as indefinite.

Applicant has corrected the antecedent basis of claim 37 to properly recite "interleukin-2" instead of cytokine. In view of this amendment, Applicant respectfully requests that the rejection of claim 37 be reconsidered and withdrawn.

Rejection of Claims Under 35 U.S.C. §103(a)

Claims 1-2 and 4-9, 12-18, 20-24, 27 and 31-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker *et al.* (*Proc. Natl. Acad. Sci.* 93:2702-2707, 1996 ("Becker") in view of Carron et al. (6,171,588) ("'588").

The present rejection is improper because the references relied on do not support a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, there must be 1) some motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to arrive at the claimed composition and use it in a method for inducing a cytocidal immune response, and 2) there must be a reasonable expectation of success. The cited prior art fails to meet these criteria in the instant case. Moreover, Applicant further submits that the claimed invention has unexpected properties, which would rebut a case of obviousness even if it were well established.

Applicant's claimed invention is directed to a method of inducing a cytocidal immune response using a combination of an immunoconjugate that includes interleukin-2 and an angiogenesis inhibitor having binding affinity for $\alpha_v\beta_3$ integrin and a composition having this combination of agents. In contrast, Becker reports the use of antibody-cytokine fusion proteins

"for the treatment of hepatic and pulmonary metastases." However, as pointed out by the Examiner, Becker does not teach compositions combining the immunoconjugate with an angiogenesis inhibitory agent. In fact, Becker fails to suggest that the disclosed immunoconjugate should be used in any combination therapy.

Becker's failure to suggest the present invention cannot be remedied by the '588 patent. The '588 patent is directed to $\alpha_v\beta_3$ monoclonal antibodies and the use of these antibodies "in methods of treating $\alpha_v\beta_3$ integrin-mediated diseases or conditions" (col. 2, lines 5-10). The Examiner argues that an ordinary artisan would have combined the teachings of Becker with the teachings of the '588 patent because the '588 patent teaches that an $\alpha_v\beta_3$ monoclonal antibody can be used with "other pharmaceutical compositions or added to established anti-cancer chemotherapeutic or biotherapeutic regimens". The Examiner refers to col. 13 of the '588 patent:

> For example, $\alpha_v\beta_3$ antibody may be co-administered or added to established anti-cancer chemotherapeutic or biotherapeutic regimens ... This may include, but is not limited to, combining or co-administering $\alpha_v\beta_3$ antibodies with cytotoxic drugs, combinations of cytotoxic drugs or with immune stimulating drugs, such as interleukins or their derivatives or with hematopoietic factors and their derivatives. For example, $\alpha_v\beta_3$ antibody may be co-administered or added to therapeutic regimens for the use IL-1, IL-2, IL-4, IL-6, IL-12, IL-15, TNF, α, β, γ interferons and M-CSF, or combinations of these agents or their derivatives, in biologic therapy of cancer. Further, $\alpha_v\beta_3$ antibody may be co-administered or added to therapeutic regimens for the use of G-CSF, M-CSF, IL-3 and erythropoietin, or combinations of these agents or their derivatives, in biologic therapy of cancer. The $\alpha_v\beta_3$ monoclonal antibodies of the present invention, or fragments thereof containing a paratope (e.g., Fab, Fab', F(ab')2 and F(v) fragments), may also be combined with cytotoxic or cytostatic drugs, protein toxins, nucleic acids or radioisotopes by methods well know to those of ordinary skill in the art. (col 13, lines 6-28).

However, Applicant submits that while the '588 patent may report that the $\alpha_v\beta_3$ antibody can be added to a number of therapeutic regimens, the '588 patent fails to mention or suggest combining the $\alpha_v\beta_3$ antibody with an immunoconjugate. Accordingly, Applicant submits that the '588 patent fails to provide the requisite motivation for one skilled in the art to combine the teachings of Becker with those of the '588 patent.

Applicant also submits that even if the cited references were combined, the combined teachings specifically fail to suggest selecting the claimed treatment regimen. Applicant submits that the Examiner is applying an improper "obvious to try" rationale in support of the obviousness rejection.

Applicant further submits that even if the cited references were combined, the combined teachings fail to provide the requisite expectation for success. Specifically, a combination of Becker and the '588 patent fails to provide a basis for expecting the beneficial results seen in the present invention.

Applicant contends that the claimed invention has unexpected properties which rebut a case of obviousness. In discussing the beneficial results of the present invention, the Examiner stated "[A]n expected beneficial result of a combination therapy is that the response induced is greater than that of either component. Thus the properties observed by Lode et al. are not unexpected." Contrary to the Examiner's position, Applicant submits that the results in Lode are unexpected. Lode does not merely show a beneficial result, Lode reports an unexpected synergistic effect when the claimed immunoconjugate is combined with an angiogenesis inhibitor having binding affinity for the $\alpha_v\beta_3$ integrin.

> The data presented here demonstrate a synergistic efficacy of simultaneous and sequential treatments specifically targeting tumor and vascular compartments of primary tumors and distant metastases. A mechanism for this synergism is provided by a decrease in blood vessel formation and an increase in inflammation only in animals treated with the combination therapy. These observations emphasize the beneficial effect of combining angiangiogenic and tumor-specific immunotherapeutic approaches. (page 1592, lines 6-11; Emphasis added).

Applicant has identified a combination therapy that not only gives beneficial results but where the agents act together to give unexpected synergy.

As evidenced by the results in Figs. 3-5 of Applicants' application and Fig. 1 in Lode, the regression in primary tumor size of mice receiving the combination treatment was dramatically significant when compared with the size of tumors receiving monotherapy. Lode reports:

> simultaneous treatments with the integrin α_v antagonist and tumor-specific antibody-IL-2 fusion proteins induced dramatic primary tumor regressions.... However, each agent used as monotherapy induced only a delay in tumor growth. [emphasis added] (see abstract in Lode).

The unexpected decrease in tumor size is reasoned in Lode to be because tumors receiving the combination therapy undergo necrosis. Fig. 3 in Lode shows that in tumors receiving combination therapy there is an unexpectedly high infiltration of leukocytes. In fact, there is nearly a five fold increase of leukocytes in tumors receiving the combination therapy relative to those tumors receiving monotherapy. Lode speculates that the influx of inflammatory cells may be the underlying reason for the unexpected finding that tumors undergoing

combination therapy become necrotic. Thus, as evidenced by Lode, Applicant submits that the combination therapy of the present invention induces a cytocidal immune response resulting in an unexpectedly high influx of leukocytes into the tumors, which cause the tumors to become necrotic and undergo a dramatic regression in size. This effect would not be expected based on the results obtained from the monotherapies. Based on these results, Applicant submits that the claimed combination therapy provides an unexpected beneficial effect.

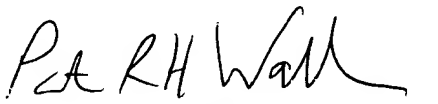
Applicant submits that independent claims 1, 12, 20, and 31, and the claims depending therefrom, are unobvious over the cited references and respectfully requests that the rejections under 35 U.S.C. § 103 be reconsidered and withdrawn.

CONCLUSION

Applicant submits that the claims 1, 2, 4-9, 12-18, 20-24, 27, and 31-37 are in condition for immediate allowance. Accordingly, Applicant respectfully requests entry as such.

Appropriate fees and forms for the RCE are submitted herewith. Applicants believe that no extension-of-time or other fee is required for this Amendment to be entered and considered. However, please consider this a conditional petition for the proper extension, if one is required, and a conditional authorization to charge any related extension or other fees necessary for entry of this paper to Deposit Account No. 20-0531.

Respectfully submitted,



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MARKED-UP VERSION OF AMENDED CLAIMS

37. (Amended) The method of claim 36, wherein the antibody binding site further comprises a CH3 domain interposed between the CH2 domain and the [cytokine] interleukin-2.